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Midazolam Pharmacodynamics and Pharmacokinetics during Acute Hypovolemia

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This study was designed to test the hypothesis that acute hypovolemia would compromise the compensatory hemodynamic mechanisms to midazolam and decrease its metabolic clearance. Experiments were performed on seven chronically instrumented female beagle dogs. Animals received a single intravenous dose of midazolam, 10 mg/kg, 4 days apart during normovolemic (N) and hypovolemic (H) states in a random sequence. Hypovolemia was achieved by the withdrawal of 26 ml/kg of blood, equivalent to one-third of the calculated blood volume. Midazolam plasma concentrations were determined at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after midazolam injection. Elimination half-life ($t_{1/2}$ β) was significantly longer and total clearance was significantly lower during H than during N. Initial distribution half-life, central compartment volume, total volume of distribution, and plasma protein binding were similar in both N and H states. Midazolam caused a significant decrease in systolic blood pressure (SBP) and an increase in heart rate (HR) during N, and produced significant decreases in SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) during H. Midazolam led to similar per cent decreases in blood pressure and cardiac output in states N and H; however, the absolute values of blood pressure and cardiac output were significantly ($P < 0.001$) lower in the hypovolemic state than in the normovolemic state. These data suggest that the hypotensive effects of midazolam, like those of other intravenous induction agents, could be potentiated by volume depletion. (Key words: Blood: volume. Hemodynamics: hypovolemia. Hypnotics: benzodiazepines; midazolam. Pharmacodynamics: midazolam. Pharmacokinetics: midazolam.)

MIDAZOLAM is a water-soluble intravenous benzodiazepine primarily used for sedation[1–3] and induction of anesthesia.[4–6] The effect of midazolam on the systemic circulation has been minimal in dogs[7,8] and humans.[9,10] A temporary increase in portal venous blood flow has been demonstrated 3 min after midazolam, suggesting an increase in venous capacitance with subsequent compensatory mobilization of splanchnic blood volume into the systemic circulation.[11] These data suggest that in hypovolemic states midazolam-induced venodilation might not be accompanied with a compensatory blood volume mobilization, resulting in reduced cardiac output and hypotension. Hypovolemia is generally accompanied by a reduction in hepatic blood flow,[12,13] which might result in a decreased drug clearance and possibly altered pharmacologic action of a high-clearance drug such as midazolam whose clearance after intravenous dosage is partly dependent on hepatic blood flow. This study was designed to test these hypotheses comparing the hemodynamic effects as well as the pharmacokinetic variables of midazolam in the chronically instrumented dog during hypovolemic and normovolemic states.

Methods

Experiments were performed on eight purebred female beagle dogs, weighing between 10 and 14 kg. Four days prior to the experiment, the dogs were anesthetized with sodium thiopental and halothane in oxygen with the use of controlled ventilation via an endotracheal tube. A size #5F pediatric Swan Ganz® catheter was inserted via the right external jugular vein and exteriorized at the back of the neck. A size #8F coronary angiographic catheter was inserted into the right femoral artery and brought out through the back of the neck by subcutaneous tunnel. These catheters were kept in a specially designed pocket of a dog jacket. Each day the dogs were returned to the laboratory for familiarization of environment, flushing catheters with heparin, and daily baseline measurements of circulatory variables. The dogs became trained to stay in the prone position on the floor without restraint. Penicillin and dehydrostreptomycin combination were given intramuscularly during the catheter insertion and once between the days of the experiment.

The dogs received 10 mg/kg of midazolam twice, 4 days apart, during normovolemic and hypovolemic states (states N and H, respectively). Hypovolemia was achieved by the withdrawal of 26 ml/kg of blood, equivalent to one-third of the calculated blood volume, within a period of 30 min. The variables were studied during

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hypovolemic and normovolemic states randomly. When the hypovolemic state was studied first, the blood was withdrawn, refrigerated in ACD solution, and retransfused after the data had been collected. Midazolam hydrochloride, dissolved in 10 ml of sterile water, was administered over a 20-s period intravenously.

Hemodynamic measurements were taken as follows: systolic and diastolic arterial blood pressures (SBP, DBP); systolic and diastolic pulmonary artery pressures (SPAP, DPAP); and pulmonary capillary wedge pressure (PCWP), all using a Grass Polygraph 7D® recorder. Duplicate cardiac outputs using 5 ml of saline at room temperature were determined with a Gould SP 1425® cardiac output computer. Heart rate was determined from the Grass® recorder. These variables were measured prior to injection, then at 2, 5, 15, 30, 45, 60, 90, 120, 150, and 180 min after midazolam administration. During the hypovolemia trial, measurements also were made prior to blood removal. Derived hemodynamic values consisted of mean arterial pressure (MAP), rate pressure product (RPP), mean pulmonary artery pressure (MPAP), stroke volume (SV), and systemic vascular resistance (SVR).

Blood samples for arterial blood gases and hemoglobin (2 ml) were withdrawn prior to midazolam and then at 5, 15, and 180 min after midazolam administration. For the blood levels of midazolam, 9 ml of arterial blood was withdrawn at time 0 (baseline prior to drug), 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after midazolam injection. The withdrawn blood was not replaced. These samples then were centrifuged and the serum removed, frozen, and analyzed by electron-capture gas-liquid chromatography.[14] These plasma levels then were fitted to an equation formed by a linear sum of exponential terms. Coefficients and exponents from the fitted function were then used to calculate the kinetic parameters of midazolam; this technique has been previously described in detail.[14,15] Midazolam protein binding was determined by equilibrium dialysis using ^{14}C labeled midazolam.[16]

All data were summarized as the mean ± standard deviation. The hemodynamic variables (HR, MAP, CO, SV) were also computed as per cent changes from the baseline (time zero) readings and summarized in a similar manner. Initial comparisons among means used a two-factor analysis of variance for a blocked design with unequal subclass numbers. Pairwise comparisons of means utilized Duncan's multiple range test.[17] Differences were considered significant if $P < 0.05$. The statistical analysis system was used for all computations.[18]

Results

Eight dogs were used in the hypovolemic part of the experiment; however, due to the accidental death of one dog after the completion of this part, only seven dogs were used in the normovolemic state experiments. Midazolam, 10 mg/kg, did not produce unconsciousness during normovolemia, regardless of whether the normovolemic state was studied first or second; however, all normovolemic dogs were slightly agitated and unable to walk or stand after midazolam. This condition was pronounced during the first 10 min after injection and subsided thereafter. The dogs completely recovered their usual state of consciousness 1 h after the midazolam injection. After phlebotomy, all dogs were recumbent and two were unconscious. Midazolam produced unconsciousness in four hypovolemic dogs for 10–30 min, and the remaining hypovolemic dogs were asleep briefly (5 to 10 min).

The hemodynamic results are presented in table 1. Prior to blood removal during the hypovolemia trial, there were no significant differences in hemodynamic values between state H and state N. Hypovolemia was accompanied by significant reductions in blood pressure, CO, PCWP, and a decrease in HR. Midazolam produced a significant decrease in SBP and an increase in HR in the normovolemic state (fig. 1) and significant decreases in SBP, DBP, and MAP (fig. 2) during the hypovolemic state. After the administration of midazolam, HR, SBP, DBP, and CO were significantly lower in the hypovolemic group during the first hour as compared with the normovolemic group; however, there were no significant differences in the per cent change in SBP, DBP, MAP, and CO between the two states (table 2).

Disappearance of midazolam from plasma was fitted by a sum of 3 exponential terms in seven of the fourteen trials and a sum of 2 exponential terms in the other seven. The number of exponential terms was unrelated to the presence or absence of hypovolemia.

Pharmacokinetic variables for midazolam during the two conditions are shown in table 3. Hypovolemia had no significant influence on the half-life of the initial rapid phase of midazolam distribution, nor on the apparent volume of the central compartment or the total volume of distribution. However, midazolam elimination half-life was significantly prolonged (3.2 *vs.* 1.9 h, $P < 0.01$), and total clearance was significantly reduced (40.8 *vs.* 63.2 ml/min/kg, $P < 0.02$) in the hypovolemic as compared with the control condition (fig. 3). Midazolam was extensively bound to plasma protein; the free fraction was not altered by hypovolemia (table 3).

Discussion

Midazolam is a benzodiazepine that has a number of pharmacologic differences relative to other currently available drugs of this class. These include water solubility in the parenteral injection formulation, rapid and more

TABLE 1. Hemodynamics of the Normovolemic and Hypovolemic Canine Model (Mean ± SD)

TIME (min)	HR	SBP	MAP	CO	SVR	PCWP
BH						
State H	132 ± 22.9	161 ± 23.0	121 ± 17.7	1.12 ± 0.35	804 ± 593	8.1 ± 1.1
BM						
State N	134 ± 20.1	166 ± 26.6	123 ± 17.4	1.09 ± 0.30	739 ± 262	6.9 ± 3.1
State H	118 ± 28.3	105 ± 36.2‡	80 ± 31.5‡	0.48 ± 0.22‡	1,304 ± 1,056‡	4.5 ± 0.9*
2						
State N	167 ± 25.8**	145 ± 26.6§	108 ± 21.1	0.94 ± 0.39	898 ± 372	6.0 ± 3.9
State H	116 ± 21.9‡	82 ± 11.7‡,¶	59 ± 9.5‡	0.39 ± 0.17‡	1,503 ± 1,030	4.3 ± 0.8
5						
State N	161 ± 24.8¶	143 ± 30.4¶	109 ± 22.5§	0.95 ± 0.29	813 ± 396	5.7 ± 4.6
State H	108 ± 20.7‡	81 ± 14.6‡,¶	58 ± 16.7‡,**	0.42 ± 0.16‡	1,389 ± 1,057‡	3.9 ± 0.6
10						
State N	154 ± 21.8§	142 ± 23.8¶	109 ± 17.3§	0.91 ± 0.27§	785 ± 591	6.1 ± 5.3
State H	106 ± 18.6‡	83 ± 14.9‡,¶	59 ± 13.1‡,**	0.44 ± 0.17‡	1,333 ± 973†	4.0 ± 0.5*
15						
State N	148 ± 29.3	139 ± 26.9¶	107 ± 19.7§	1.02 ± 0.46	708 ± 492	6.4 ± 4.7
State H	105 ± 19.2‡	85 ± 16.7‡,§	61 ± 17.7‡,¶	0.49 ± 0.20‡	1,273 ± 1,198‡	3.9 ± 0.6*
30						
State N	145 ± 32.2	145 ± 20.0§	112 ± 14.5	1.01 ± 0.41	514 ± 206	7.5 ± 4.8
State H	111 ± 18.7‡	94 ± 15.7‡	70 ± 15.1‡	0.51 ± 0.20‡	1,159 ± 994†	4.1 ± 0.8†
45						
State N	144 ± 30.2	146 ± 23.2§	115 ± 18.4	1.00 ± 0.49	615 ± 371	6.3 ± 2.9
State H	118 ± 22.6†	96 ± 11.8‡	71 ± 12.0‡	0.54 ± 0.20‡	892 ± 862§	5.0 ± 2.6
60						
State N	149 ± 26.7	146 ± 17.5§	116 ± 11.6	1.08 ± 0.45	686 ± 353	6.6 ± 3.4
State H	122 ± 23.5†	98 ± 12.1‡	73 ± 12.4‡	0.55 ± 0.19‡	1,099 ± 831*	4.1 ± 0.8*
90						
State N	143 ± 19.8	145 ± 10.6§	116 ± 8.6	1.04 ± 0.37	716 ± 349	6.7 ± 4.2
State H	136 ± 30.8§	104 ± 11.7	78 ± 9.9‡	0.59 ± 0.23‡	1,079 ± 833*	4.3 ± 1.0*
120						
State N	143 ± 23.9	152 ± 14.3	118 ± 15.2	1.07 ± 0.42	666 ± 402	7.6 ± 4.5
State H	148 ± 27.6**	108 ± 14.1‡	82 ± 14.6‡	0.66 ± 0.31‡,§	1,061 ± 795*	4.4 ± 0.9†
150						
State N	153 ± 23.8§	154 ± 22.6	120 ± 17.9	1.10 ± 0.36	722 ± 389	7.1 ± 4.1
State H	150 ± 26.2**	114 ± 14.3‡	85 ± 12.0‡	0.63 ± 0.25‡	1,035 ± 604*	5.1 ± 2.8
180						
State N	149 ± 25.9	153 ± 21.4	119 ± 17.5	1.10 ± 0.35	664 ± 197	7.0 ± 3.8
State H	154 ± 23.3**	116 ± 15.1‡	88 ± 13.0‡	0.73 ± 0.24‡,¶	903 ± 523§	5.1 ± 2.4

N = normovolemic state (n = 7); H = hypovolemic state (n = 8); BH = before hemorrhage (values observed in dogs of state H before hypovolemia was induced); BM = before midazolam injection (for state N—immediately before the injection, and for state H—after hypovolemia was induced; immediately before the injection of midazolam); HR = heart rate (beats/min); SBP = systolic blood pressure (mmHg); MAP = mean arterial pressure (mmHg); CO = cardiac output (l/min); SVR = systemic vascular resistance (dyn·s·cm^{-5}); PCWP = pulmonary capillary wedge pressure (mmHg); BH = before hemorrhage.

* $P < 0.05$ *versus* normovolemic state.
† $P < 0.01$ *versus* normovolemic state.
‡ $P < 0.001$ *versus* normovolemic state.
§ $P < 0.05$ *versus* values at time 0 at corresponding state.
¶ $P < 0.01$ *versus* values at time 0 at corresponding state.
** $P < 0.001$ *versus* values at time 0 at corresponding state.

predictable onset, shorter duration of action, and a significantly shorter half-life and higher clearance.[19] Cardiovascular stability of midazolam has been shown in healthy humans[20] as well as those with coronary artery disease.[9,10,21-23] A comparative hemodynamic study revealed that midazolam produces slightly greater decreases in blood pressure and systemic vascular resistance than diazepam.[10] In a previous canine study, this hypotensive effect of midazolam apparently resulted from venodilation and was compensated by peripheral (splanchnic) blood mobilization into the central circulation.[11] The influence of volume depletion on the pharmacokinetics and pharmacodynamics of midazolam has not been evaluated systematically, and the purpose of this study was to examine the hemodynamic and pharmacokinetic changes produced by midazolam in acute hypovolemic dogs. The following hypotheses were tested: 1) acute hypovolemia compromises the compensatory hemodynamic responses to midazolam; and 2) hypovolemia decreases the clearance and alters the time-course of action of midazolam.

A chronic awake dog experimental design that used each animal as its own control for data analysis was chosen as the experimental model. This model permitted examination of the effects of midazolam on the smallest number of subjects and allowed us to conduct the study

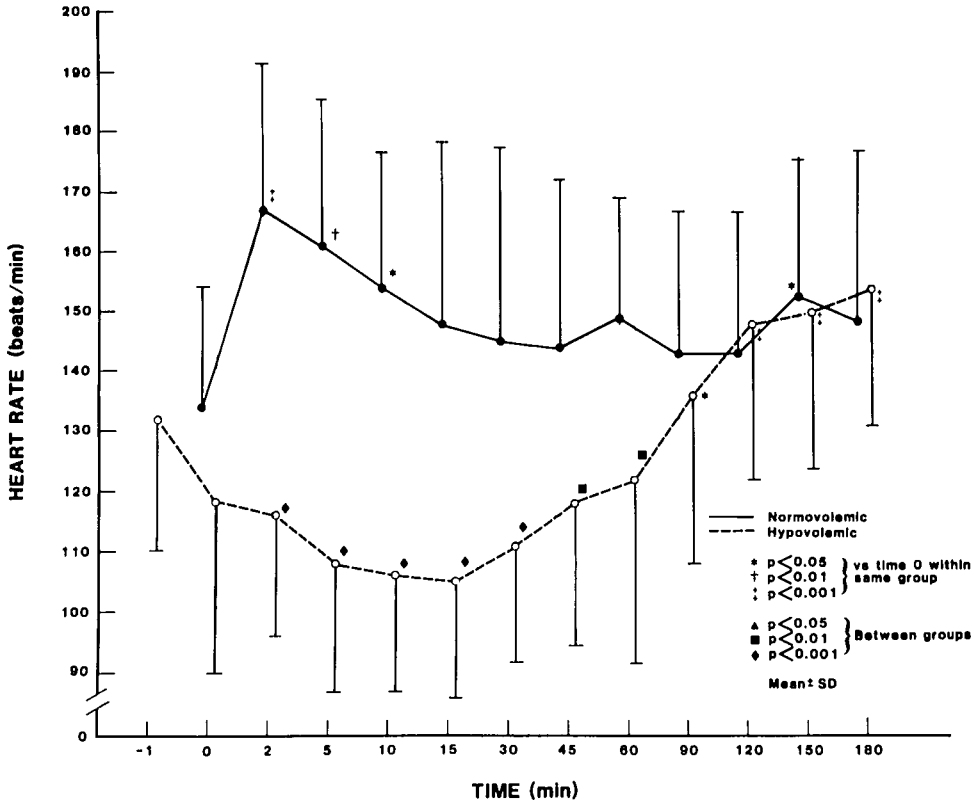

FIG. 1. Heart rate after midazolam injection at time 0 during normovolemic and hypovolemic states. Note that midazolam did lead to a decrease in heart rate during hypovolemia and an increase in heart rate during the normovolemic state.

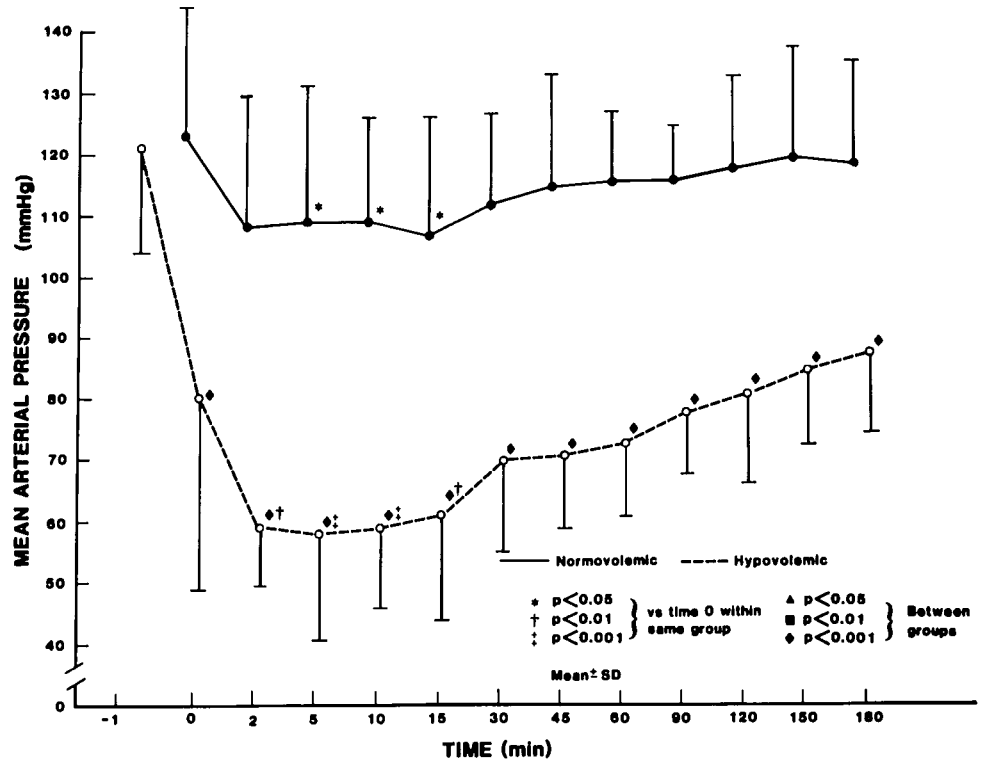

FIG. 2. Mean arterial pressure after midazolam injection during both hypovolemic and normovolemic states. Note that midazolam did lead to more severe hypotension during the hypovolemic state than during the normovolemic state.

TABLE 2. Per cent Changes of the Normovolemic and Hypovolemic Canine Model (Mean ± SD)

Time (min)	HR	MAP	CO	SV
2				
State N	+19.0 ± 11.1	−14.3 ± 8.7	−24.4 ± 20.7	−36.9 ± 15.9
State H	−1.6 ± 13.7†	−12.2 ± 25.1	−4.5 ± 20.7	−1.6 ± 24.9†
5				
State N	+22.7 ± 25.9	−12.4 ± 10.6	−20.7 ± 24.6	−27.2 ± 12.5
State H	−7.7 ± 10.6‡	−22.9 ± 18.7	−5.6 ± 23.5	+3.9 ± 29.6*
10				
State N	+17.3 ± 23.6	−11.4 ± 10.0	−14.7 ± 20.3	−27.4 ± 9.6
State H	−8.3 ± 15.6‡	−21.5 ± 17.2	−0.2 ± 26.5	+11.6 ± 37.1†
15				
State N	+12.8 ± 27.6	−13.7 ± 10.6	−5.4 ± 38.9	−17.3 ± 17.5
State H	−9.2 ± 14.3‡	−19.3 ± 17.9	+7.7 ± 25.8	+21.2 ± 37.2†
30				
State N	+10.5 ± 28.3	−9.2 ± 7.0	−8.2 ± 23.6	−15.9 ± 19.7
State H	−4.4 ± 11.5*	−6.6 ± 21.6	+14.6 ± 35.8	+22.3 ± 46.7†
45				
State N	+10.2 ± 28.2	−6.6 ± 7.7	−9.6 ± 29.6	−19.3 ± 14.3
State H	+1.0 ± 14.9	−3.4 ± 29.6	+22.9 ± 38.9*	+26.2 ± 54.8‡
60				
State N	+13.1 ± 19.9	−5.3 ± 5.7	−2.6 ± 23.5	−14.3 ± 14.7
State H	+5.1 ± 16.2	−1.1 ± 29.5	+23.5 ± 38.3	+20.9 ± 46.8†
90				
State N	+9.2 ± 20.7	−5.2 ± 9.2	−5.6 ± 21.8	−13.5 ± 13.2
State H	+16.9 ± 25.4	+8.2 ± 33.3	+30.0 ± 36.6*	+17.9 ± 51.3*
120				
State N	+8.5 ± 17.8	−3.3 ± 11.2	−4.1 ± 19.3	−10.9 ± 16.5
State H	+27.2 ± 20.1	+11.9 ± 32.0	+46.7 ± 42.1†	+17.2 ± 37.4*
150				
State N	+16.0 ± 20.8	−2.4 ± 12.0	+1.1 ± 16.6	−11.0 ± 18.1
State H	+29.4 ± 20.5	+16.2 ± 35.0	+44.6 ± 44.1†	+12.6 ± 32.3*
180				
State N	+12.3 ± 17.8	−3.2 ± 10.9	−1.7 ± 8.7	+11.5 ± 12.5
State H	+33.7 ± 25.1*	+19.9 ± 37.5*	+72.8 ± 71.9‡	+30.1 ± 49.3‡

Values are mean per cent change ± SD relative to time zero in corresponding state. N = normovolemic state (n = 7); H = hypovolemic state (n = 8).

* $P < 0.05$ *versus* N at corresponding stage (min).
† $P < 0.01$ *versus* N at corresponding stage (min).
‡ $P < 0.001$ *versus* N at corresponding stage (min).

without the confounding variable of another anesthetic. The acute hemorrhage of 30% of estimated blood volume is a standard acute hypovolemia model.[24–26] In our experiments, the amount of blood withdrawn during the hypovolemic state before midazolam injection was 26 ml/kg, followed by another 8–9 ml/kg of blood taken over a period of 12 h for purposes of analyses of blood gases, hemoglobin, and midazolam concentrations. Both normovolemic and hypovolemic animals had the same amount of blood withdrawn for analyses. Therefore, the observed pharmacodynamic and pharmacokinetic differences between both states were due to acute phlebotomy (26 ml/kg of blood withdrawn over 30 min) in our experimental model. The stability of the model is seen with the nearly identical baseline hemodynamic variables whether dogs were phlebotomized before or after their exposure to midazolam (table 1).

Although the same dose of midazolam was adminis-

TABLE 3. Pharmacokinetic Parameters for Midazolam in the Normovolemic and Hypovolemic Canine Model (mean ± SD)

	Initial Distribution Half-life ($t_{1/2}\alpha$)(min)	Elimination Half-life ($t_{1/2}\beta$)(h)	V_1 (l/kg)	V_d (l/kg)	Clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	Protein Binding (% bound)
State N	14.3 ± 11.2	1.9 ± 0.9	1.6 ± 1.5	8.8 ± 4.6	63.2 ± 17.6	95.9 ± 3.2
State H	15.5 ± 8.5	3.2 ± 1.8*	1.7 ± 1.1	10.9 ± 5.0	40.8 ± 25.9*	95.6 ± 2.3

Where N = normovolemic state (n = 7); H = hypovolemic state (n = 7); $t_{1/2}\alpha$ = initial distribution half-life; $t_{1/2}\beta$ = elimination half-life; V_1 = apparent volume of central compartment; V_d = total apparent volume of distribution.

* Significantly different from normovolemic state ($P < 0.02$).

tered for each of the two trials on a given animal, central nervous system (CNS) depressant effects were more pronounced in the hypovolemic state. Our study does not establish the mechanism of the increased CNS depressant effect of midazolam associated with hypovolemia. It is unlikely to be explained by altered pharmacokinetics, since the initial distribution half-life, the central compartment volume, and the total volume of midazolam distribution—all of which are important determinants of the time-course and intensity of central depressant effect[27]—were not significantly changed by hypovolemia. In any case, similar findings were described by Weiskopf and associates,[26] who reported that hypovolemia (reduction of 30% estimated blood volume) reduced the "anesthetic requirement" 33% and 40% for thiopental and ketamine, respectively.

In this study, midazolam produced a decrease in blood pressure with a compensatory increase in heart rate in normovolemic animals. This is consistent with previous laboratory studies.[8,11] Acute hypovolemia produced significant reductions in blood pressure, cardiac output, and pulmonary capillary wedge pressure, and the administration of midazolam further reduced blood pressure. Midazolam administration produced a significant (23%) decrease in MAP in the hypovolemic animals and a significant (12%) decrease in the normovolemic dogs (table 1); however, the difference between states in relative decreases in MAP did not reach a level of statistical significance (table 2). Although the relative percent decreases in the MAP were not statistically different, the MAP after midazolam in hypovolemic animals was significantly lower than in the normovolemic animals because of the 30% reduction of blood volume. Therefore, hypovolemic dogs experienced more profound hypotension than normovolemic animals (fig. 2).

Interestingly, there was a significant difference in heart rate response to midazolam in the two states. There was a slight decrease in heart rate 5 min after midazolam during hypovolemia (−8%), whereas the heart rate increased during normovolemia (23%) (fig. 1). This cannot be explained by an initial tachycardia in the hypovolemic groups, since before midazolam (table 1) hypovolemic animals actually had a heart rate of 118 beats/min compared with a normovolemic heart rate of 134 beats/min ($P > 0.05$). It appears that the normal heart rate response (increase) to midazolam is attenuated or eliminated by hypovolemia. A decrease in HR during hypotension produced by sodium nitroprusside has also been observed.[28] These unexpected changes in heart rate remain unexplained.

In healthy humans, the pharmacokinetic profile of midazolam is characterized by a large volume of distribution (1–2 l/kg), short elimination half-life (1–4 h), high total metabolic clearance (5–10 ml · min · kg^{-1}), and

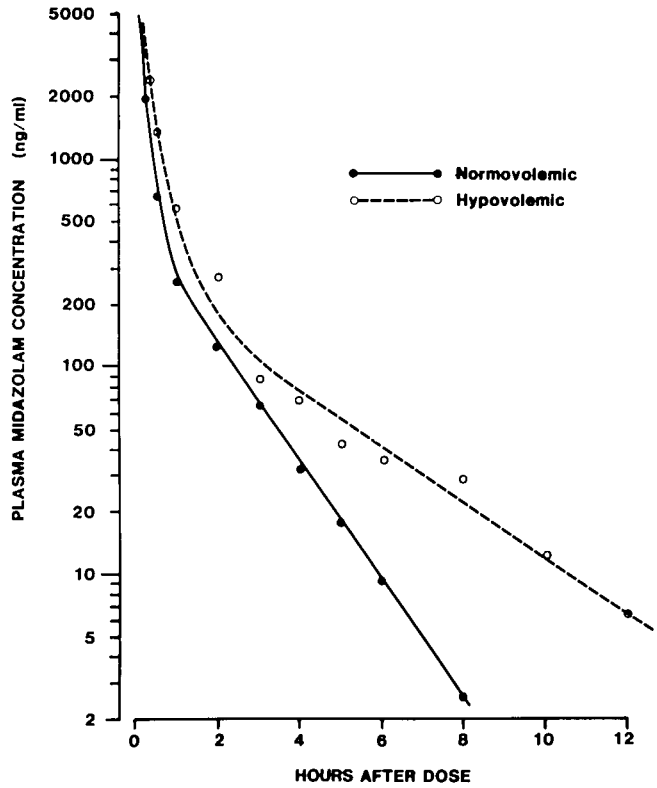

FIG. 3. Plasma midazolam concentrations in a representative animal following intravenous midazolam administration in the control (normovolemic state) and during hypovolemia.

extensive plasma protein binding (96–97% bound).[14,19,29] Due to its high hepatic clearance, more than 50% of an oral dose is extracted during the first pass through the liver.[29] In dogs, midazolam has even more extensive distribution and higher hepatic clearance relative to body weight than in humans. Thus, a reduction in hepatic blood flow, as might occur due to hypovolemia,[12,13] would be expected to reduce the total clearance of a drug such as midazolam with high and therefore flow-dependent clearance.[30] This, in turn, might alter the pharmacodynamic profile of midazolam. In the present study, hypovolemia did significantly reduce the metabolic clearance of midazolam by 35% and prolonged elimination half-life by 68%. Since midazolam protein binding was not different between control and hypovolemic conditions, the reduced clearance and prolonged half-life were not attributable to altered plasma binding.

The changes in midazolam half-life and clearance due to hypovolemia appeared to have no relation to the duration of midazolam's hemodynamic effects. The time-course of the hemodynamic changes following intravenous midazolam were similar in both hypovolemic and normovolemic states. This finding is not surprising, since the rate and extent of drug distribution, as opposed to elimination half-life and clearance, appear to be the

most important determinants of pharmacodynamic effects following single intravenous doses of benzodiazepines such as midazolam.[27] Although hypovolemia prolonged midazolam's elimination half-life and clearance, the initial distribution half-life, central compartment volume, and total volume of distribution were unchanged.

In summary, hypovolemia reduced total drug clearance and prolonged the elimination half-life of midazolam. Acute hypovolemia did not markedly alter the hemodynamic response to midazolam administration. However, after midazolam injection, CO and MAP were lower during hypovolemia than during the normovolemic state. Therefore, it seems that midazolam should be given with caution to hypovolemic humans.

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